

This Listing and Amendment of the Claims supersedes all prior versions

LISTING AND AMENDMENTS OF THE CLAIMS:

1. (Currently Amended) A method for the determination of adrenomedullin-the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a biological fluid sample from ~~release in a human, comprising measuring the level in said a biological fluid sample of said human of said mid-proAM the mid-regional partial peptide of proadrenomedullin (mid-pro-AM) which consists of~~ has the sequence of SEQ ID NO: 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring uses a monoclonal or polyclonal antibody which in each case is specific only to said partial peptide.

2. (Currently Amended) The method according to claim 2126, wherein the mid-proAM~~mid-pro-AM~~ in the biological fluid is measured in an immunoassay wherein~~which operates with~~ at least one of said antibodies~~labeled antibody~~ which specifically recognize~~recognizes~~ a sequence of mid-proAM~~is labeled~~.

3. (Currently Amended) The method according to claim 2, wherein said immunoassay using said labeled antibody~~the immunoassay is an assay further employing~~ with a solid phase-bound competitor for the mid-proAM~~mid-pro-AM and a labeled antibody or a sandwich assay further employing, in which at least two~~

~~antibodies~~ at least one additional antibody which specifically ~~binds~~ bind to a different partial ~~sequence~~ sequences of mid-proAM (SEQ ID NO: 3) from that bound by said ~~labeled antibody~~ are used.

4. (Currently Amended) The method according to claim ~~21~~ 26, wherein the level of circulating mid-proAM (SEQ ID NO: 3) is determined and the biological fluid is plasma or serum.

5. (Currently Amended) The method according to claim 3, wherein both antibodies bind to a region of mid-proAM which extends from the amino acid 60 to the amino acid 94 of preproadrenomedullin ~~the pre-proAM~~.

6. (Currently Amended) The method according to claim 3, wherein all said antibodies are monoclonal and/or polyclonal.

7. (Currently Amended) The method according to claim 3, wherein all said antibodies are affinity-purified polyclonal antibodies.

8. (Currently Amended) The method according to claim 3, wherein for ~~all~~ said sandwich assay ~~assays~~, one of the antibodies is obtained by immunization of an animal with an antigen which contains a synthetic peptide sequence which comprises the amino acids 69-86 of pre-proAM (SEQ ID NO: 4), and the other of the antibodies

is obtained by immunization with an antigen which contains a synthetic peptide sequence which comprises the amino acids 83-94 of pre-proAM (SEQ ID NO: 5).

9. (Currently Amended) The method according to claim 3, wherein for said sandwich assay~~all said assays~~, one of the antibodies is labeled and the other antibody is bound to a solid phase or is not bound to a solid phase but can be subsequently bound thereto during the assay~~, or one is labeled and not bindable to a solid phase and the other can be bound to a solid phase.~~

10. (Currently Amended) The method according to claim 3, wherein for said sandwich assay~~assays~~, both the first and the second antibodies are present dispersed in a liquid reaction mixture and a first labeling component which is part of a labeling system based on fluorescence or chemiluminescence extinction or amplification is bound to the first antibody, and a second labeling component of said labeling system is bound to the second antibody so that, after binding of both antibodies to the mid-proAM to be detected, a measurable signal which permits detection of the resulting sandwich complexes is generated.

11. (Previously Presented) The method according to claim 10, wherein the labeling system comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

12. (Canceled)

13. (Withdrawn and Currently Amended) The method according to claim ~~21~~42, wherein the ~~said~~ determination of ~~adrenomedullin release~~ is carried out as part of a multiparameter determination for diagnosis of sepsis in which at least one further parameter relevant for sepsis diagnosis is also ~~determined at the same time~~.

14. (Withdrawn and Previously Presented) The method according to claim 13, wherein the further parameter or parameters relevant for sepsis diagnosis is or are anti-ganglioside antibodies, procalcitonin, CA 125, CA 19-9, S100B, S100A proteins, LASP-1, soluble cytokeratin fragments, inflammin, CHP, a peptide prohormone other than pro-AM, glycine-N-acyltransferase, carbamoylphosphate synthetase 1 or C-reactive protein or a fragment thereof.

15. (Canceled)

16. (Currently Amended) The method according to claim ~~21~~45, wherein the ~~said~~ determination of ~~adrenomedullin release~~ is carried out in the course of a multiparameter determination for diagnosis of cardiac disease in which further parameters relevant for cardiac diagnosis are also determined.

17. (Canceled)

18. (Withdrawn and Currently Amended) The method according to claim ~~21~~47, wherein the ~~said~~ determination of ~~adrenomedullin release~~ is carried out in the course

of a multiparameter determination for a diagnosis of cancer in which further parameters relevant for cancer diagnosis are also determined.

19. (Currently Amended) A method for the determination of adrenomedullin release ~~the mid-regional partial peptide of proadrenomedullin (mid-proAM)~~ in a human, comprising measuring the level in a biological fluid sample of said human of said mid-proAM ~~the mid-regional partial peptide of proadrenomedullin (mid-pro AM)~~ which consists of ~~has~~ the sequence of SEQ ID NO:3 ~~NO-3~~ and ~~which consists of~~ ~~amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1);~~ said level of ~~the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human,~~ wherein said measuring uses a monoclonal or polyclonal antibody which in each case is specific to an epitope in said partial peptide sequence ~~and not to any other epitope of pro-adrenomedullin.~~

20. (Currently Amended) ~~The~~A method of claim 1 wherein said measuring is not accomplished using a competitive radioimmunoassay.

21. (Currently Amended) A method for the determination of adrenomedullin release ~~the mid-regional partial peptide of proadrenomedullin (mid-proAM)~~ in a human, comprising measuring the level in a biological fluid sample of said human of said mid-proAM ~~the mid-regional partial peptide of proadrenomedullin (mid-pro AM)~~ which consists of ~~has~~ the sequence of SEQ ID NO:3 ~~NO-3~~ and ~~which consists of amino~~

~~acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is by immunoassay which is not accomplished using a competitive radioimmunoassay.~~

22. (Currently Amended) A method for the determination of ~~adrenomedullin release~~ the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human, comprising measuring the level in a serum or plasma ~~biological fluid sample~~ of said human of said mid-proAM ~~the mid-regional partial peptide of proadrenomedullin (mid-pro-AM) which consists of~~ has the sequence of SEQ ID ~~NO:3~~ NO-3 ~~and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is of the circulating level of said mid-proAM partial peptide circulating in the blood of a patient from whom said sample~~ fluid is taken.

23. (Currently Amended) ~~The~~ A method of claim 22 wherein when said measured level of said partial peptide in said sample is a fluid from a patient suffering from sepsis, said measured level has an order of magnitude ~~which is greater than the order of magnitude of 2X of 12 times~~ said level in a healthy person.

24. (Currently Amended) A method of claim 22 where said determination is used for diagnosis, prognosis or therapy-accompanying monitoring of a disease associated with an increased level of adrenomedullin, other than sepsis, to be carried out together with consideration of other parameters from said human relevant to said disease ~~human is not suspected of suffering from sepsis.~~

25. (Currently Amended) A method for the determination of ~~adrenomedullin release~~ the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human, comprising measuring the level in a biological fluid sample of said human of said mid-proAM ~~the mid-regional partial peptide of proadrenomedullin (mid-pro AM)~~ which ~~consists of~~ has the sequence of SEQ ID ~~NO:3~~ NO-3 and which ~~consists of~~ is ~~amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is by antibody sandwich assay employing at least two antibodies specific to epitopes in said partial peptide sequence.~~

26. (Currently Amended) A method for the determination of ~~adrenomedullin release~~ the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human for diagnosis, prognosis or therapy-accompanying monitoring of ~~suspected of having a disease, other than sepsis, associated with an increased level of adrenomedullin in a human to be carried out together with consideration of other parameters from said human relevant to said disease~~ release, comprising measuring the

level of said mid-proAM ~~the mid-regional partial peptide of proadrenomedullin (mid-pro-AM)~~ which consists of ~~has~~ the sequence of SEQ ID NO:3, using an antibody specific to said mid-proAM ~~NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1)~~, said level of said mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human.

27. (Currently Amended) A method for the diagnosis, prognosis or therapy-
accompanying monitoring of a disease, other than sepsis, which is associated with an increased level of adrenomedullin release in a human to be carried out together with consideration of other parameters from said human relevant to said disease, comprising measuring the level in a biological fluid of said human of the mid-regional partial peptide of proadrenomedullin (mid-proAM) ~~(mid-pro-AM)~~ which consists of ~~has~~ the sequence of SEQ ID NO:3 ~~NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1)~~, and correlating said level of said mid-regional partial peptide with the presence of said disease.

28. (Currently Amended) The ~~A~~ method of claim 27 wherein said disease is a cancer or a cardiac disease.

29. (Currently Amended) The ~~A~~ method of claim 27 wherein said disease is a cardiac disease.

30. (Withdrawn and Currently Amended) ~~The~~A~~n~~ isolated polypeptide consisting of the amino acid sequence SEQ ID NO:~~3~~~~NO-3~~.

31. (Currently Amended) ~~The~~A method of claim 19 wherein said measuring is not accomplished using a competitive radioimmunoassay.

32. (Currently Amended) A method for the determination of ~~adrenomedullin~~ release—the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human, comprising measuring the level in a biological fluid sample of said human of ~~said mid-proAM~~ the mid-regional partial peptide of proadrenomedullin (mid-pro-AM) which ~~consists of~~has the sequence of SEQ ID NO:~~3~~~~NO-3~~ and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is conducted using an immunoassay which does not employ ~~not accomplished—an antibody against the partial peptide 66-113 of preproadrenomedullin using a radioimmunoassay requiring an extraction step.~~

33. (New) A method for the indirect determination of adrenomedullin in a human, comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide of proadrenomedullin (mid-proAM) which consists of the sequence of SEQ ID NO:3, said mid-proAM level correlating with the level of adrenomedullin.

34. (New) A method for the determination of the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human, comprising measuring the level in a biological fluid sample of said human of said mid-proAM which consists of the sequence of SEQ ID NO:3, wherein when said sample is serum from a patient suffering from sepsis, said level measured has an order of magnitude of 12 times said level in a healthy person.

35. (New) A method for the determination of the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human, comprising measuring the level in a biological fluid sample of said human of peptide bound by an antibody specific to said mid-proAM which consists of the sequence of SEQ ID NO:3.

36. (New) A method of claim 35 wherein said measuring is by antibody sandwich assay.

37. (New) A method of claim 35 wherein said antibody is monoclonal.

38. (New) A method of claim 35 wherein when said sample is serum from a patient suffering from sepsis, said measured level has an order of magnitude of 12 times said level in a healthy person.

39. (New) A method of diagnosis, prognosis or therapy-accompanying monitoring of a disease associated with an increased level of adrenomedullin in a

human to be carried out together with consideration of other parameters from said human relevant to said disease, comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide of proadrenomedullin (mid-proAM) which consists of the sequence of SEQ ID NO:3 by an antibody specific to said mid-proAM.

40. (New) The method of claim 22 wherein said measuring is not accomplished using a competitive radioimmunoassay.

41. (New) The method of claim 26 wherein said measuring is not accomplished using a competitive radioimmunoassay.

42. (New) The method of claim 27 wherein said measuring is not accomplished using a competitive radioimmunoassay.

43. (New) A method for the determination of the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human, comprising measuring the level in a biological fluid sample of said human of said mid-proAM which consists of the sequence of SEQ ID NO:3, wherein said measuring is by an immunoassay using a specific binding partner for an epitope in said mi-proAM.

44. (New) The method of claim 43 wherein said measuring is not accomplished using a competitive radioimmunoassay.

45. (New) A method of claim 1 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

46. (New) A method of claim 19 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

47. (New) A method of claim 21 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

48. (New) A method of claim 22 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

49. (New) A method of claim 25 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

50. (New) A method of claim 26 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

51. (New) A method of claim 27 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

52. (New) A method of claim 32 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

53. (New) A method of claim 33 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

54. (New) A method of claim 34 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

55. (New) A method of claim 35 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

56. (New) A method of claim 39 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

57. (New) A method of claim 43 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

58. (New) A method of claim 1 further comprising removing from a human said sample to be measured.

59. (New) A method of claim 19 further comprising removing from a human said sample to be measured.

60. (New) A method of claim 21 further comprising removing from a human said sample to be measured.

61. (New) A method of claim 22 further comprising removing from a human said sample to be measured.

62. (New) A method of claim 25 further comprising removing from a human said sample to be measured.

63. (New) A method of claim 26 further comprising removing from a human said sample to be measured.

64. (New) A method of claim 27 further comprising removing from a human said sample to be measured.

65. (New) A method of claim 32 further comprising removing from a human said sample to be measured.

66. (New) A method of claim 33 further comprising removing from a human said sample to be measured.

67. (New) A method of claim 34 further comprising removing from a human said sample to be measured.

68. (New) A method of claim 35 further comprising removing from a human said sample to be measured.

69. (New) A method of claim 39 further comprising removing from a human said sample to be measured.

70. (New) A method of claim 43 further comprising removing from a human said sample to be measured.